REMARKS

Claims 7-22 were pending in the application. Claims 7 and 8 have been amended and claim 11 has been cancelled. Support for the amendments to the claims can be found in the specification and claims as filed. Accordingly, after the amendments presented herein have been entered, claims 7-10 and 12-22 will remain pending. No new matter has been added.

Rejection of claims under 35 USC 103

The Examiner has maintained the rejection of claims 7-10, 14, 15 and 20-22 as being unpatentable over Sasse et al. in view of Greenwald. Applicants respectfully traverse this rejection.

Applicant has prepared further experimental data, the results of which are provided with the enclosed Declaration under 37 CFR 1.132. These results in combination with the results filed with the Declaration of November 30, 2006 reveal that by coupling tubulysin A with a PEG ester, amide or phenol, the activity of the respective compounds in two cancer cell lines can be dramatically reduced, thus, leading to tubulysin derivatives with lower toxicity. As a consequence, the object of the present invention as indicated in paragraph [0004] of the present specification is solved with the compounds according to claim 7.

Furthermore, it is pointed out that Greenwald classifies PEG-drugs in permanently bonded PEG-drugs (cf. chapter 2, page 160) and non-permanently bonded PEG-drugs, i.e. PEG prodrugs (chapter 3, page 160).

According to Greenwald, permanently bonded PEG-drugs comprise PEG linkers of molecular weight 2000 to 5000, i.e. low molecular weight PEG. As can be taken from the Declaration filed November 30, 2006, tubulysin A PEG-derivatives having a PEG linker with high molecular weight, such as 35kDa or 40kDa provide better results with regard to the object of the present invention than low molecular weight PEGs. This finding is by no means rendered obvious by Greenwald suggesting to use permanently bonded PEG-drugs wherein the PEG linker has a molecular weight of from 2000 to 5000. On the contrary, the teaching of Greenwald teach away from the instant invention and would divert a person skilled in the art from the teaching of the present invention.

As mentioned above, chapter 3 of the Greenwald publication, PEG prodrugs are disclosed. Greenwald states that a prodrug is a biologically inactive derivative of a parent drug molecule that usually requires an enzymatic transformation within the body in order to release the active drug, and has improved delivery properties over the parent molecule (cf. page 160, right-hand column, last paragraph). In other words, a prodrug is formed in order to render a parent drug molecule in a condition to enable absorption of the drug molecule in the human body. Once the prodrug has entered the human body, it is enzymatically transformed to release the active drug.

However, this scenario does not apply to the tubulysin derivatives according to the present invention. As stated in paragraph [0003] of the present specification, tubulysins possess an extremely high cytotoxicity. If the tubulysin derivatives released free tubulysins immediately after absorption in the human body, the free tubulysins would immediately exert their cytotoxic effects resulting in extensive cell death of normal cells. As a consequence, such tubulysin prodrugs are not selective and are connected with serious side effects. As stated in paragraph [0004] of the present specification, the object of the present invention is to enhance selectivity of tubulysins.

Applicant has surprisingly found that tubulysin derivatives according to claim 7 are stable in plasma/buffer and, thus, less cytotoxic than natural tubulysins as indicated above with regard to the experimental data provided with the Declaration dated November 30, 2007 and the additional experimental data provided with the enclosed Declaration. Furthermore, applicant has surprisingly found that once the tubulysin derivatives have entered a cancer cell, free tubulysin is released and can exert its high cytotoxic activity directly in the cancer cell. Accordingly, the compounds according to the present invention provide for drug targeting of tubulysin selectively to cancer cells. These findings are by no means rendered obvious by the publications of Sasse in combination with Greenwald.

Furthermore, as can be taken from the poster attached to the enclosed Declaration, tubulysin derivatives additionally comprising a cyclodextrin group solve the object of the present invention. In fact, cyclodextrin-PEG-polymer conjugates of tubulysin show high antiproliferative activity in human cancer cells (cf, table 1), but are significantly less toxic than tubulysin A (cf. table 2). As evident from table 3 and graph 1, cyclodextrin conjugates of tubulysin are better tolerated than vinblastine and tubulysin A and lead to a significant increase

in tumor growth delay, inhibit the formation of new tumor cells and at the same time reduce the number of existing tumor cells. It is again pointed out that the Sasse publication does not pertain to tubulysin conjugates and that the Greenwald publication does not disclose cyclodextrin conjugates at all. As a consequence, the claimed invention is by no means rendered obvious by the publications of Sasse in and Greenwald.

Rejection of Claims 12, 13, and 16-19 Under 35 USC 112, First Paragraph

The Examiner has maintained the rejection of claims 12, 13, and 16-19 under 35 USC 112, first paragraph as not being enabling. While in no way acquiescing to the validity of the Examiner's rejection, and solely in the interest of expediting prosecution, Applicants have amended the claims to overcome this rejection.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

Rejection of Claims 7-10 and 12-22 Under 35 USC 112, First Paragraph

The Examiner has maintained the rejection of claims 7-10 and 12-22 under 35 USC 112, first paragraph as not complying with the written description requirement. While in no way acquiescing to the validity of the Examiner's rejection, and solely in the interest of expediting prosecution, Applicants have amended the claims to overcome this rejection. Applicants reserve the right to pursue the claims as originally filed in this or a continuing application.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

REMARKS

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Dated: August 6, 2007

Respectfully submitted,

By _____

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